

Agenda

- Prognosis and biology
- Adjuvant therapy
- Neoadjuvant therapy
- Post-Neoadjuvant therapy
- Minimal Residual Disease

TNBC: Challenges and Opportunities

- TNBC lacks expression of ER, PR, HER2
- Accounts for 15% to 20% of all breast cancers
- Difficult-to-treat subtype that is highly heterogeneous
- Survival time is shorter than for other subtypes
- Because of lack of therapeutic targets, cytotoxic chemotherapy is standard treatment
- Emerging data in TNBC management may affect treatment strategies in the future

Prognosis in early stage TNBC

15,000 patients in NCCN database

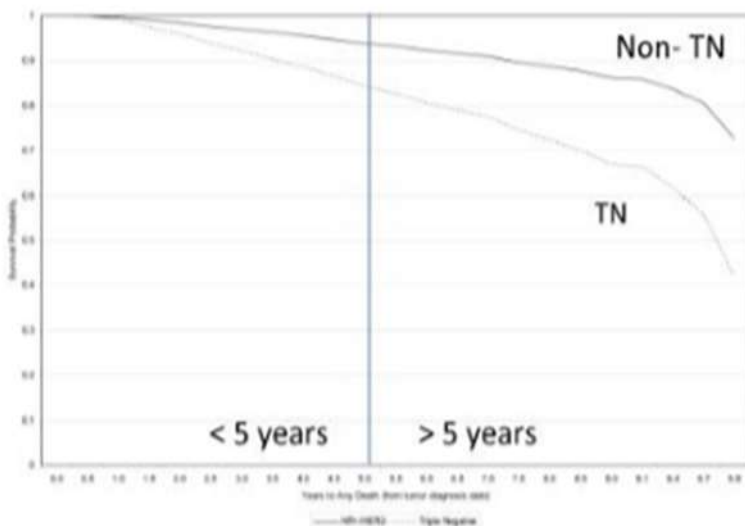


Figure 1.
Overall Survival by Tumor Subtype (HR+/HER2- versus Triple Negative) Adjusting for Age, Stage, Race, Receipt of Chemotherapy, Tumor Size, Histologic Grade and Nodal Status

Lin, Cancer 2012

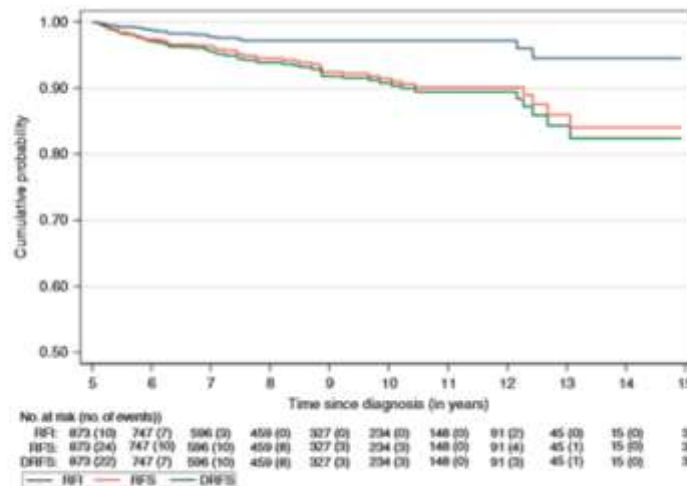


Figure 2. Recurrence-free interval (RFI), recurrence-free survival (RFS), and distant relapse-free survival (DRFS) of triple-negative breast cancer 5-year survivors as function of time from diagnosis.

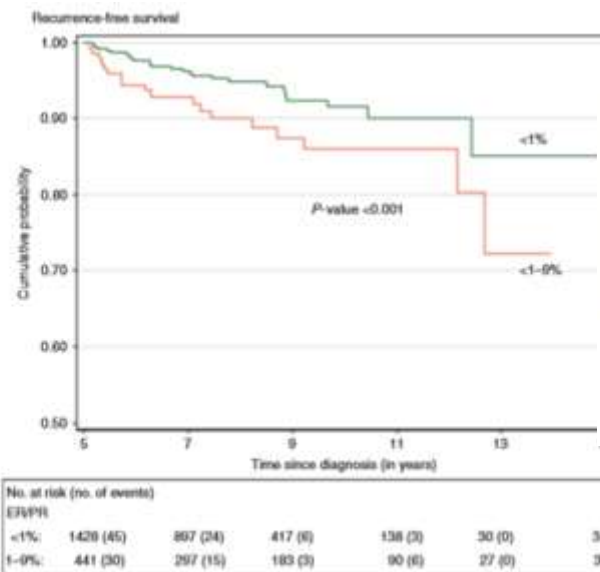


Figure 3. Recurrence-free survival of triple-negative breast cancer 5-year survivors as function of hormone receptor positivity and time from diagnosis. ER = oestrogen receptor; PR = progesterone receptor.

Outcomes for patients with TNBC alive at 5 years post-dx at MDACC

By low level estrogen receptor expression

Reddy, BJC, 2017

Biology of TNBC

Biological subtypes of TNBC

- Basal-like 1, 2
- Immuno-modulatory
- Mesenchymal
- Mesenchymal Stem-Like
- Luminal Androgen Receptor

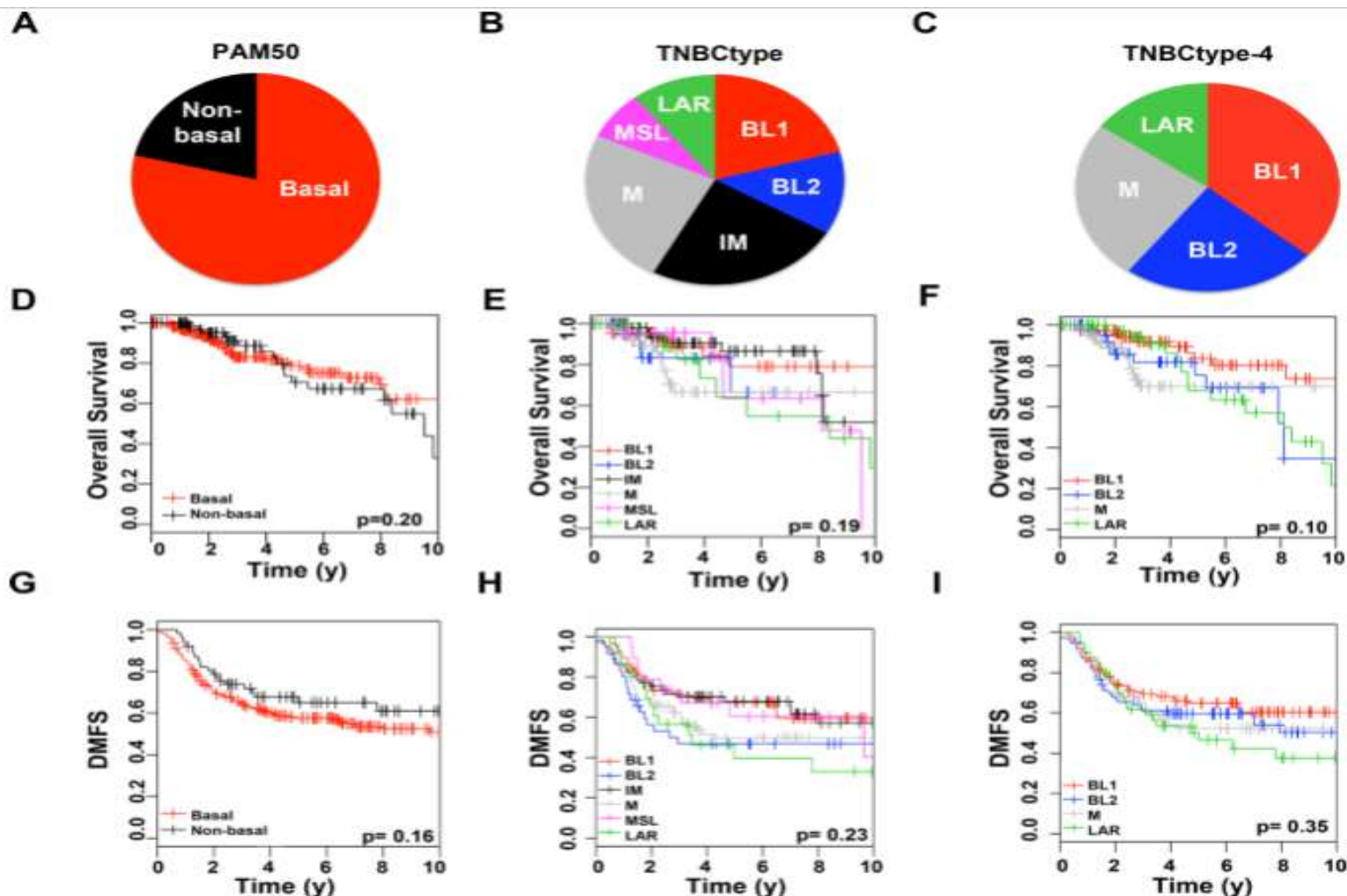


Fig 3. Molecular subtype distribution and survival analysis of TNBC samples stratified by PAM50, TNBCtype or refined TNBCtype-4. Piecharts show the distribution of 767 TNBC samples by (A) PAM50 (B) TNBCtype or (C) refined TNBCtype-4. Kaplan-Meier curves show overall survival for TNBC patients stratified by (D) PAM50 (E) TNBCtype or (F) refined TNBCtype-4 or relapse-free survival stratified by (G) PAM50 (H) TNBCtype or (I) refined TNBCtype-4. P-values shown were determined by logrank test. * indicates significant ($p<0.05$) pairwise survival differences between a subtype and all other subtypes combined not adjusted for multiple comparisons.

BRCA mutations and DNA repair deficiency in TNBC

- 80-90% of BRCA1 mutated tumors are TNBC or basal-like subtype
- “BRCA-ness” signatures define additional TNBC with DNA-repair deficiency
- Sensitivity to PARP inhibitors and platinum agents

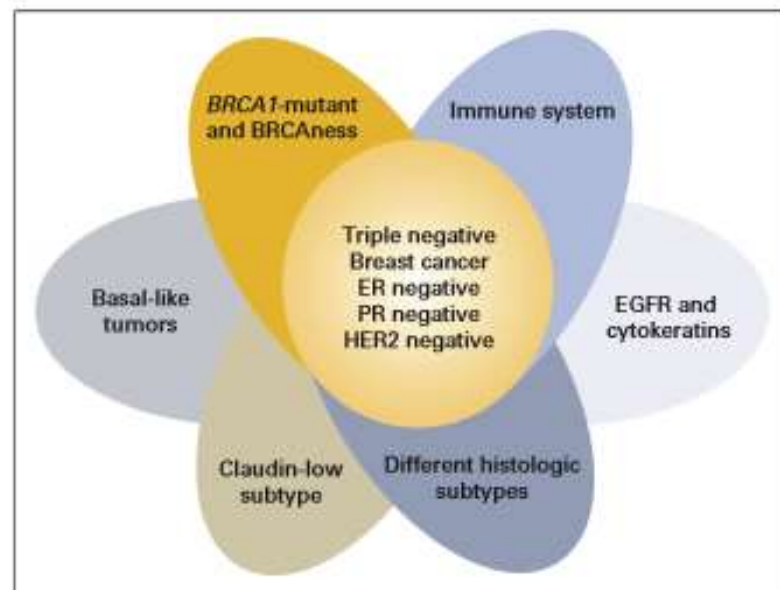
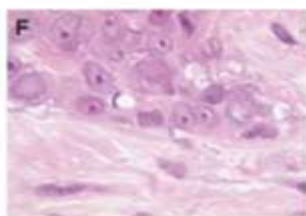


Fig 1. Heterogeneities in the nomenclature and classification of triple-negative breast cancer. EGFR, epidermal growth factor receptor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

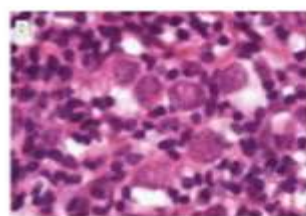
Metzger-Filho, Tutt, JCO, 2012

Immune infiltration predicts response in TNBC

Pretherapeutic core biopsy samples from a total of 1058 patients (GeparDuo-GeparTrio)

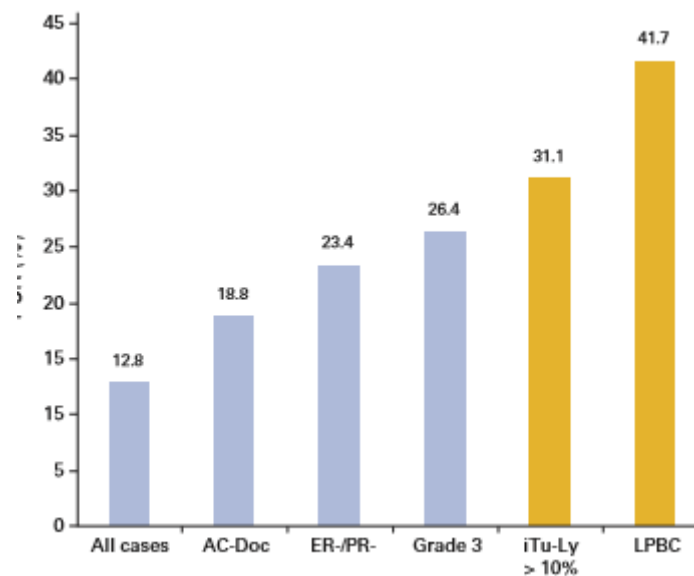


No infiltrate



Lymphocyte predominant breast cancer (LPBC)

High degree of correlation between stromal and intratumor lymphocytes



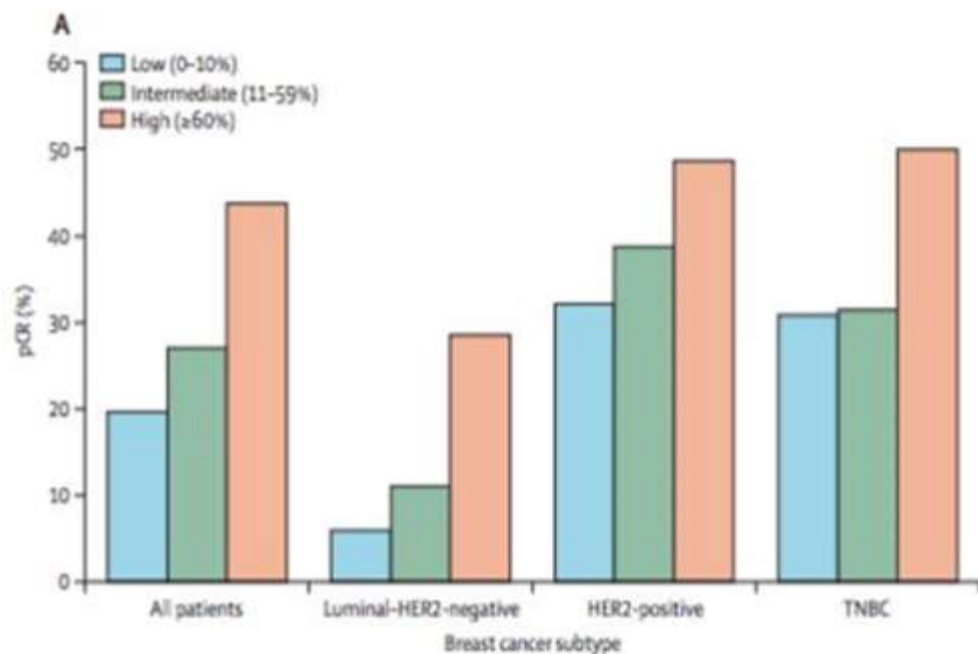
Immune infiltration predicts response in TNBC

Combined data from 6 neoadjuvant trials

In the TNBC subtype, pCR was achieved in

- **31%:** low TILs (0-10%)
- **31%:** intermediate TILs (11-59%)
- **50%:** high TILs (>60%)

($p < 0.001$)



Denkert, Lancet Oncology, 2018

New context in TNBC adjuvant setting

Journal of Clinical Oncology[®]

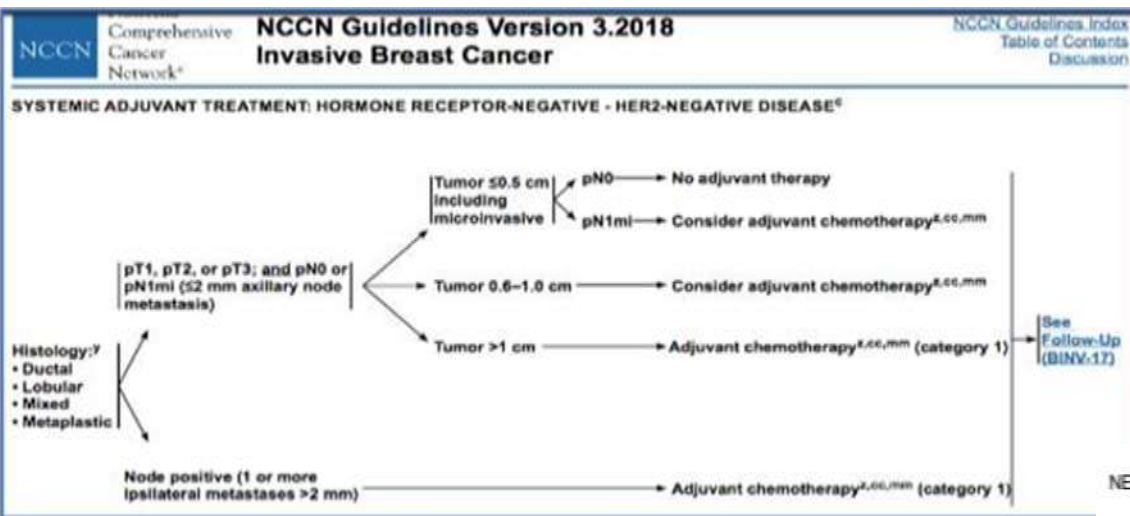
An American Society of Clinical Oncology Journal

ORIGINAL REPORTS | Breast Cancer

Tumor-Infiltrating Lymphocytes and Prognosis: A Pooled Individual Patient Analysis of Early-Stage Triple-Negative Breast Cancers

Strong prognostic role of sTILs in early-stage TNBC and excellent survival of patients with high sTILs after adjuvant chemotherapy and supports the integration of sTILs in a clinicopathologic prognostic model for patients with TNBC

Adjuvant Therapy: Chemotherapy is still standard of care



HER2-Negative⁶

- Preferred regimens:
 - Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks⁷
 - Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel⁷
 - TC (docetaxel and cyclophosphamide)
- Useful in certain circumstances:
 - Dose-dense AC (doxorubicin/cyclophosphamide)
 - AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
 - CMF (cyclophosphamide/methotrexate/fluorouracil)
 - AC followed by weekly paclitaxel
- Other recommended regimens:
 - AC followed by docetaxel every 3 weeks
 - EC (epirubicin/cyclophosphamide)
 - TAC (docetaxel/doxorubicin/cyclophosphamide)

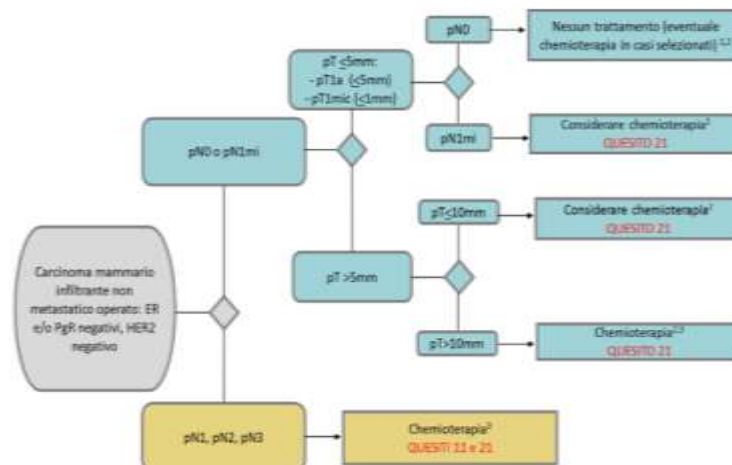
NEOPLASIE DELLA MAMMELLA

LINEE GUIDA
2018



Anthracyclines, Taxanes,
Dose-dense scheduling

Figura 7 – Carcinoma mammario infiltrante NON METASTATICO OPERATO ER e/o PgR NEGATIVO, HER2 NEGATIVO: Terapia sistemica adiuvante



What will improve outcomes in early TNBC?

- Not delayed initiation of adjuvant chemotherapy
- Platinum and/or PARP inhibitors
- Immunotherapy

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Delayed initiation of adjuvant



Impact of the delayed initiation of adjuvant chemotherapy in the outcomes of triple negative breast cancer

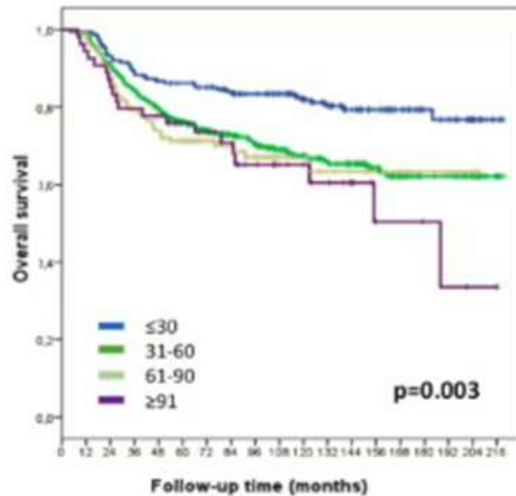
Zaida Morante, MD, Rossana Ruiz, MD, Gabriel de la Cruz – Ku, MD, Fernando Namuche, MD, Raul Mantilla, Maria Guadalupe Luján, MS, Hugo Fuentes, MD, Jesus Schwarz, MD, Alfredo Aguilar, MD, Silvia Neciosup, MD-PhD, Henry Gomez, MD-PhD



- 6, 827 women diagnosed with BC stages I to III.
- TTC 61 days after surgery was associated with adverse outcomes.
 - **Stage II** → DFRS (HR, 1.20; 95% CI: 1.02 to 1.43)
 - **Stage III** → OS (HR, 1.76; 95% CI: 1.26 to 2.46), RFS (HR, 1.34; 95% CI: 1.01 to 1.76) and DFRS (HR, 1.36; 95% CI: 1.02 to 1.80)
- TNBC/HER-2 patients who started chemotherapy 61 days after surgery had worse survival.
 - **TNBC** → (HR, 1.54; 95% CI, 1.09 to 2.18)
 - **HER-2** → (HR, 3.09; 95% CI, 1.49 to 6.39)

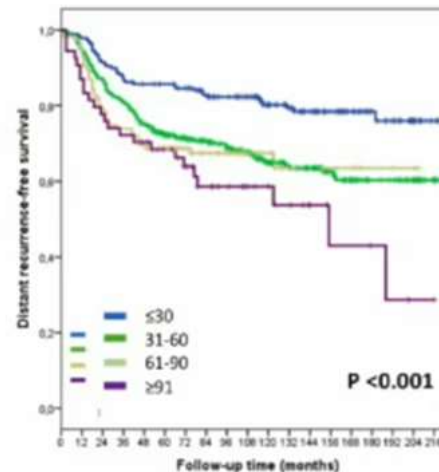
Delayed initiation of adjuvant chemotherapy

Overall survival estimated curves by TTC



Overall survival					
TTC (days)	Total	Events	12mo	60mo	120mo
≤30	189	37	99.5%	86.2%	82%
31-60	329	105	98.8%	76.2%	67.4%
61-90	115	37	97.4%	71.3%	67.1%
≥91	54	20	94.4%	75.8%	65.1%

Distant disease-free survival estimated curves by TTC



Distant disease-free survival					
TTC (days)	Total	Events	12mo	60mo	120mo
≤30	189	39	97.9%	85.7%	80.2%
31-60	329	112	94.5%	72.2%	64.9%
61-90	115	38	93%	68.7%	67.5%
≥91	54	24	87%	68.4%	58.6%

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- **Platinum** and/or PARP inhibitors
- Immunotherapy

Platinum agents in early stage TNBC

Study	Design	N	pCR	
			Control	Platinum
GeparSixto	nplDox/Pac/Bev +/- wCb (AUC1.5) x 16 wks	315	42.7%	53.2%
Alliance 40603	wPac +/- Cb (AUC 6) +/- Bev → AC (2x2 design)	433	41%	54%
GEICAM/2006-03	EC → Doc +/-Cb(AUC6)	94	30%	30%
I-SPY 2	wPac +/- Cb/Veliparib → AC	71	26%(est)	52%(est)
NCC-Japan	wPac +/- Cb(AUC5) → CEF	75	26%	62%
Univ of Kansas	Cb(AUC6)/Doc x 6 vs AC x 4 → T x 4	92	42%	65%
BrighTNess	wP +/- Cb +/- Veliparib → AC x 4	634	31%	57% (53% with V)
WSG-ADAPT TN	wnab-Pac + Cb(AUC2) or Gem D1/8 q3 wks x 4	336	-	45% vs 28%
Sharma et al	Cb(AUC6) + Doc x 6	190	-	55%

➤ Increased toxicities with add-on approach

Impact on long-term outcomes?

➤ Response biomarkers ?

Platinum agents in early stage TNBC

Tested in neoadjuvant setting: CALGB 40603 and GeparSixto

	CALGB 40603	GeparSixto
Sample Size	443	315
pCR rates	54% vs. 41%	53.2% vs. 36.9%
pCR Benefit	13%	16%
3-year EFS in Control Arm	71.6%	76.1%
3-year EFS in Carbo Arm	76.5%	85.8%
Carbo EFS/DFS Benefit	4.9%	9.7%
EFS HR (CI)	0.84 (0.58-1.22)	0.56 (0.33-0.96)

To whom shall we give a platinum

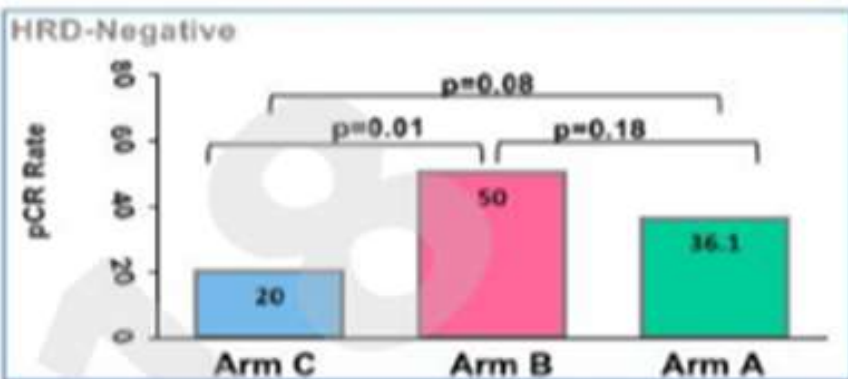
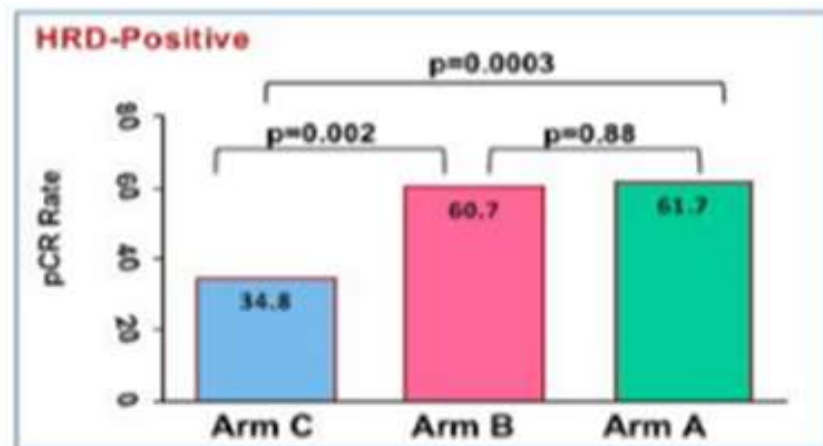
Addition of Carboplatin	CALGB 40603	GeparSixto
Higher discontinuation rate	✓	✓
More dose reductions	✓	✓
Reduction in median total dose intensity		✓
Higher grade 3, 4 toxicity	✓	✓
Neutropenia	✓	✓
Thrombocytopenia	✓	✓
Anemia		✓
GI toxicity		✓

- Toxicity led to high degree of dose reduction/discontinuation in platinum arms
- Consider in healthy, highest risk population

What will improve outcomes in early TNBC?

- Not delayed initiation of adjuvant chemotherapy
- Platinum and/or **PARP inhibitors**
- Immunotherapy

Targeting DNA damage repair with PARP inhibitors

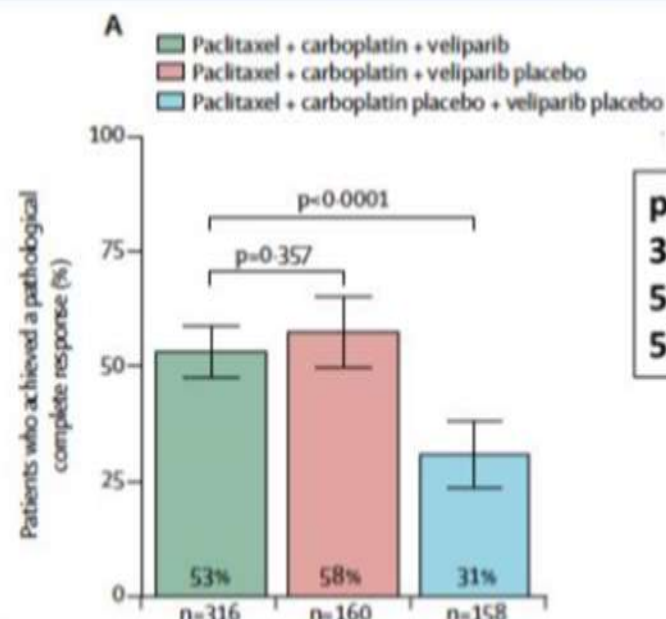


BrighTNess Trial

3 arms: Pac>AC

Pac/carbo>AC

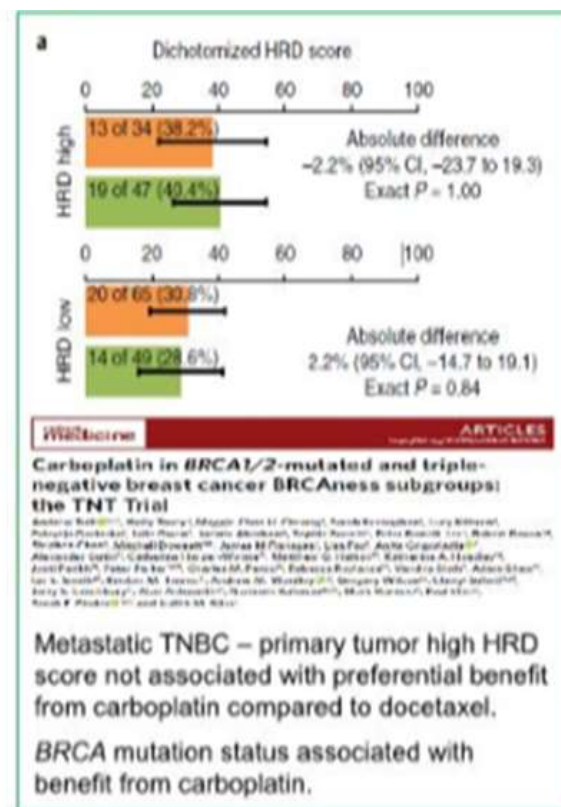
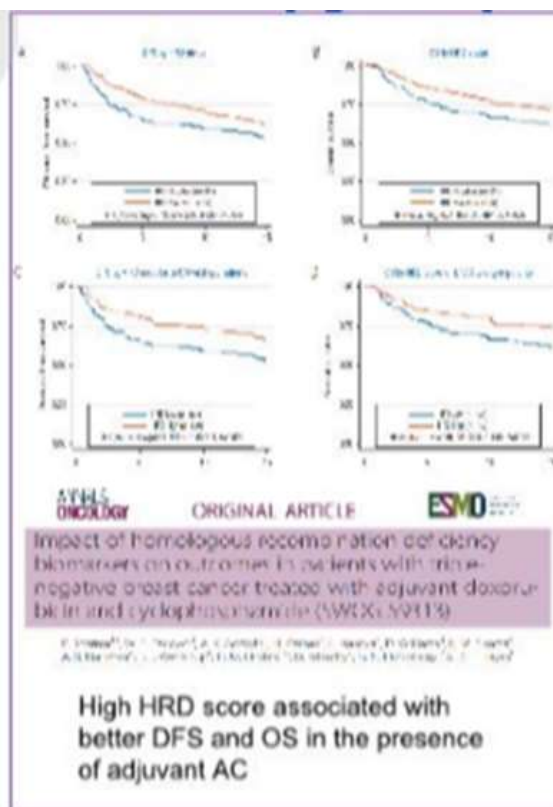
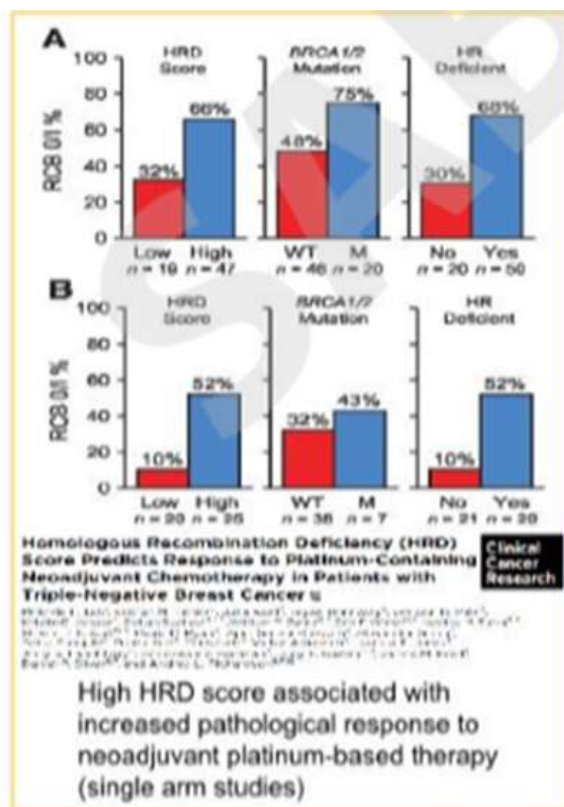
Pac/carbo/veliparib>AC



pCR:
31%
58%
53%

Loibl,
Lancet
Oncology,
2018

Homologous recombination deficiency in TNBC and chemotherapy response











To whom shall we give a platinum?

Why the higher pCR rate in BrighTNess?

	CALGB 40603	GeparSixto	BrighTNess
Sample Size	443	315	634
pCR Benefit	13%	16%	27%
Control therapy	Sequenced	Concurrent	Sequential
Anthracycline	240 / 12 wks	360 x/18 wks	240 / 12 wks
Taxane	960 / 12 wks	1440 /18 wks	960 / 12 wks
Cyclophosphamide	Yes	No	Yes
Carboplatin dose/schedule	AUC 6 q 3 weeks	AUC 2 or 1.5 weekly	AUC 6 q 3 weeks
Taxol/carbo completion/DI	64%	70%	88%

Await BrighTNess survival analysis

Ongoing neo/adjuvant PARP/platinum trials

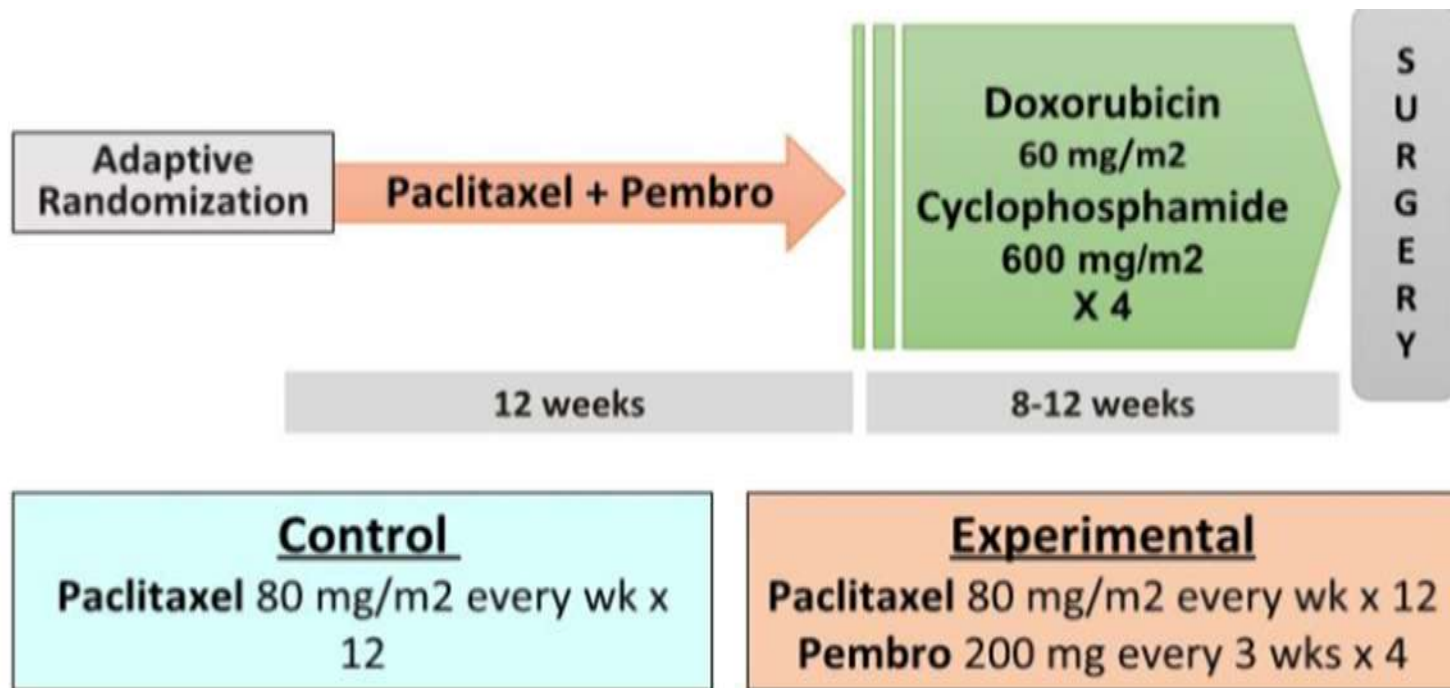
Trial details	Phase	NCT number
poly(ADP-ribose)polymerase (PARP) inhibitors		
 Adjuvant olaparib in patients with germline BRCA-associated HER2-negative early-stage breast cancer (OlympiA)	III	NCT02032823
 Neoadjuvant carboplatin and paclitaxel plus olaparib in TNBC and/or germline BRCA-mutated HER2-negative breast cancer (PARTNER)	II/III	NCT03150576
Adjuvant radiotherapy +/- olaparib in patients with non-metastatic inflammatory breast cancer who have received neoadjuvant chemotherapy (SWOG S1706)	II	NCT03598257
 Neoadjuvant talazoparib in germline BRCA1/2-mutated early-stage TNBC	II	NCT03499353
 Neoadjuvant niraparib in patients with early-stage HER2-negative breast cancer with BRCA1/2 mutation	I	NCT03329937
 Paclitaxel plus olaparib vs paclitaxel/carboplatin followed by EC as neoadjuvant chemotherapy in patients with HER2-negative early breast cancer and homologous recombination deficiency (GeparOla)	II	NCT02789332
Platinum agents		
 Adjuvant AC followed by paclitaxel +/- carboplatin in early-stage TNBC (NRG-BR003)	III	NCT02488967
Adjuvant treatment of EC followed by weekly taxane +/- carboplatin in early-stage TNBC (TCTN)	III	NCT02455141
Doxorubicin and cyclophosphamide followed by taxane +/- carboplatin as (neo)adjuvant therapy in early-stage TNBC (PEARLY)	III	NCT02441933
Adjuvant platinum vs capecitabine in stage II-III TNBC patients who have basal-like residual disease after neoadjuvant taxane +/- anthracycline chemotherapy (ECOG-ACRIN 1131)	III	NCT02445391
 Four cycles of neoadjuvant cisplatin versus four cycles of AC in germline BRCA-mutated early-stage HER2-negative breast cancer (INFORM)	II	NCT01670500
 Assessment of the ability of the homologous recombination deficiency assay (HRD™, Myriad) to predict pathological complete response to cisplatin vs weekly paclitaxel in early-stage TNBC patients (TBCRC030)	II	NCT01982448
Addition of neoadjuvant carboplatin to paclitaxel, followed by AC/EC, in large operable or locally advanced TNBC	III	NCT03168880

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What will improve outcomes in early TNBC?

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- **Immunotherapy**

I-SPY 2 TRIAL: Pembro 4 Arm Schema



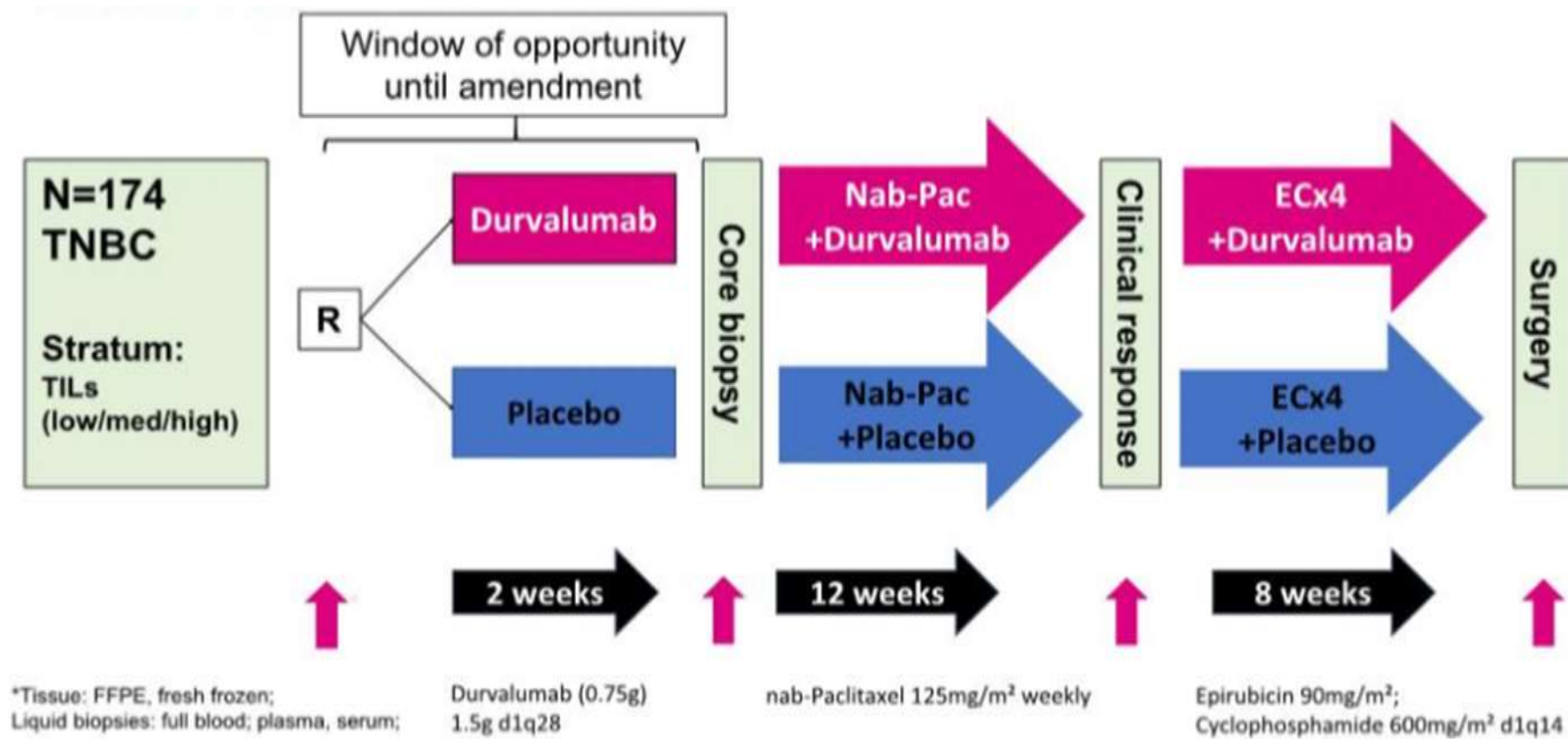
Pembrolizumab graduated in all HER2- signatures: 3-Fold increase in pCR in both HR+/HER2- and TNBC

Signature	Estimated pCR Rate (95% Probability Interval)		Probability Pembro Superior to Control	Predictive Probability of Success in Phase 3
	Pembro	Control		
HER2-	0.44 (0.33 – 0.55)	0.17 (0.11 – 0.23)	>0.999	0.985
HR-HER2-	0.60 (0.44 – 0.75)	0.22 (0.13 – 0.30)	>0.999	0.996
HR+HER2-	0.30 (0.17 – 0.43)	0.13 (0.07 – 0.19)	0.996	0.834

The Bayesian model estimated pCR rates appropriately adjust to characteristics of the I-SPY 2 population.
The raw pCR rates (not shown) are higher than the model estimate of 0.604 in TNBC.

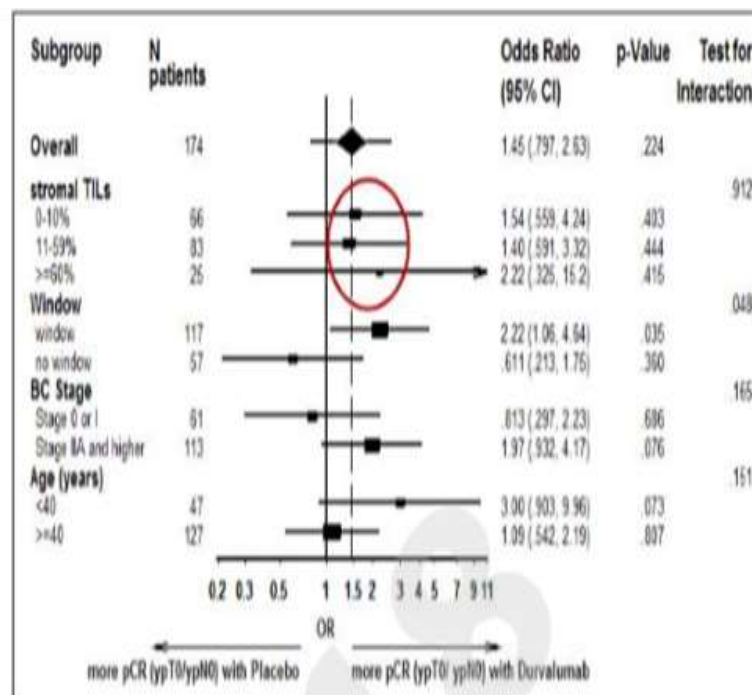
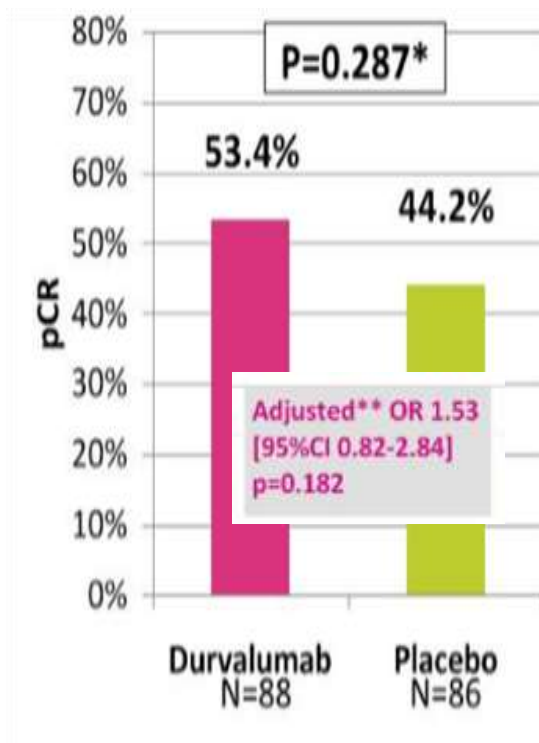
Nanda, ASCO, 2017

GeparNUEVO Study Design



Aimed to observe an improvement in pCR of 48% → 66%

GeparNUEVO Primary endpoint





mRNA Signatures Predict Response to Durvalumab Therapy in Triple Negative Breast Cancer (TNBC) – Results of the Translational Biomarker Programme of the neoadjuvant double-blind placebo controlled GeparNuevo trial

Loibl S¹, Sinn BV², Kam T³, Untch M⁴, Treu D⁵, Sinn HP⁶, Weber K⁷, Hanusch C⁸, Fasching PA⁹, Huober J¹⁰, Zahm M¹¹, Jakobsch C¹², Thomalla J¹³, Blohmer JU¹⁴, Marmé F¹⁵, Klauschen F¹⁶, Rhiem K¹⁷, Feider B¹⁸, von Minckwitz G¹⁹, Burchard N²⁰, Schneeweiss A²¹, Denkert C²²

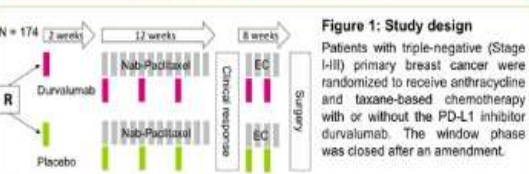
¹German Breast Group, Neu-Isenburg, Germany; ²Department of Pathology, Charité-Universitätsmedizin Berlin, Berlin, Germany; ³Department of Gynecology, Universitätsklinikum Frankfurt, Frankfurt, Germany; ⁴Nicolaus-Klinikum Berlin-Buch, Berlin, Germany; ⁵Department of Pathology, Universitätsklinikum Heidelberg, Heidelberg, Germany; ⁶Department of Gynecology, Robert-Koch-Institut München, München, Germany; ⁷Department of Gynecology, Universitätsklinikum Ulm, Ulm, Germany; ⁸Department of Gynecology, Uniklinik Köln, Köln, Germany; ⁹St. Marien-Klinik Offenburg, Offenburg, Germany; ¹⁰St. Marien-Klinik Offenburg, Offenburg, Germany; ¹¹St. Marien-Klinik Offenburg, Offenburg, Germany; ¹²St. Marien-Klinik Offenburg, Offenburg, Germany; ¹³St. Marien-Klinik Offenburg, Offenburg, Germany; ¹⁴St. Marien-Klinik Offenburg, Offenburg, Germany; ¹⁵St. Marien-Klinik Offenburg, Offenburg, Germany; ¹⁶St. Marien-Klinik Offenburg, Offenburg, Germany; ¹⁷St. Marien-Klinik Offenburg, Offenburg, Germany; ¹⁸St. Marien-Klinik Offenburg, Offenburg, Germany; ¹⁹St. Marien-Klinik Offenburg, Offenburg, Germany; ²⁰St. Marien-Klinik Offenburg, Offenburg, Germany; ²¹St. Marien-Klinik Offenburg, Offenburg, Germany; ²²St. Marien-Klinik Offenburg, Offenburg, Germany



Background

The GeparNuevo trial showed an increase in the pCR rate to 53% vs 44%; $p=0.287$ compared to placebo in TNBC with the addition of the anti-PD-L1 antibody durvalumab to a neoadjuvant anthracycline-taxane containing chemotherapy [1]. In a predefined subgroup analysis, a significant increase of the pCR rate was observed for patients that received durvalumab for 2 weeks alone prior to the start of chemotherapy (window phase; 61% vs 41%, p interaction=0.048), while pCR rate was not in patients who started durvalumab together with chemotherapy.

Patients and Methods



Patients and Samples: Diagnosis and ER, PR, Ki-67 and HER2-status were confirmed centrally prior to randomization. Negative hormone receptor status was defined as ER staining in < 1% of tumor cells and PR staining in < 10%, negative HER2 status as an IHC score of 0, 1+, or 2+ without amplification (ratio < 2 or < 6 copies/cell) in SISH. Pathologic complete response (pCR) was defined as the absence from cancer in the breast and lymph nodes (ypT0 ypN0).

Targeted RNA Sequencing: 162 pre-therapeutic formalin-fixed, paraffin-embedded core biopsies were available for profiling of 2559 genes using the HTG EdgeSeq® system (HTG Oncology biomarker panel) that combines a nuclease protection assay with next generation sequencing. Data were processed as recommended by HTG, median normalized within each sample and across the experiment, and log2-transformed. For differential gene expression analyses, data was scale-normalized and linear models were fit after filtering for minimal expression (> 4) and variability ($IQR > 1$). We used logistic regression analyses to evaluate the predictive value of a predefined gene signature of tumor-infiltrating lymphocytes (CXCL9, CCL5, IC01, CXCL13) [2], a previously described signature for response to immune-checkpoint inhibition (IFNG, CD274, LAG3, CXCL9) [3] and a metagene for cytotoxic response (PRF1, GZMA). We calculated molecular breast cancer subtypes using the AIMS [4] approach.

Results

Parameter	Category	N	Percent
cT	cT1-2	152	94
	cT3-4	10	6
cN	cN-	112	69
	cN+	50	31
Grade	G2	28	17
	G3	134	83
Ki-67	< 30 %	22	14
	≥ 30 %	140	86
Lymphocytes	LPBC	24	15
	No LPBC	138	85
Response	pCR	82	51
	RD	80	49
Arm	Durvalumab	83	51
	Placebo	79	49
Window	yes	106	65
	no	56	35

Table 1: Baseline characteristics, treatment and response

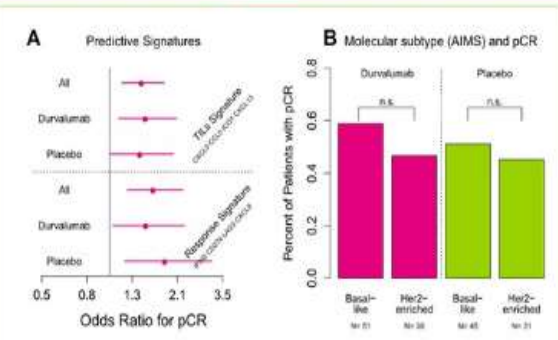


Figure 2: Predefined signatures and molecular subtypes

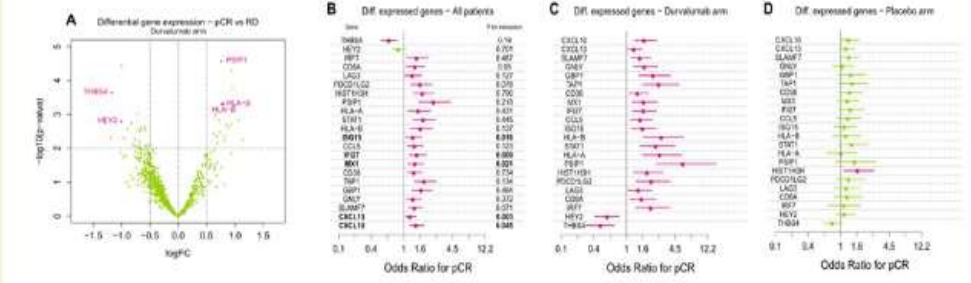


Figure 3: Differential gene expression analysis according to treatment response
A: Differential gene expression analysis according to pCR vs. residual disease (RD) after neoadjuvant treatment with immune-checkpoint inhibition. B-D: Logistic regression analysis for treatment response for 20 genes with increased expression ($\log_{2}FC > 0.5$ and $P < 0.01$) and two exemplary genes with decreased expression according to response. B: across all patients with interaction P value according to treatment and within C: the durvalumab and D: placebo arms, respectively. Five genes are significantly predictive and may be interesting markers for response to durvalumab.

- The predefined signatures for TILs and response to immune-checkpoint blockade were predictive for pCR. However, the effect was not specific for the durvalumab arm (Fig. 2A). The cytotoxic metagene was not associated with response (not shown).
- The molecular tumor subtype (AIMS) was not predictive (Fig. 2B). 5 cases were classified as normal-like or Luminal A, showing no differences in response (not shown).

Conclusions

- Predefined signatures reflecting tumor immune response predict response to neoadjuvant chemotherapy, but not specifically to durvalumab
- Differential gene expression analysis according to response reveals signatures of immune response
- A subset of genes might be specifically predictive for durvalumab and might serve as a basis to define predictive tests in the future
- Further validation is ongoing.
- The basal-like molecular subtype is not associated with response in this study

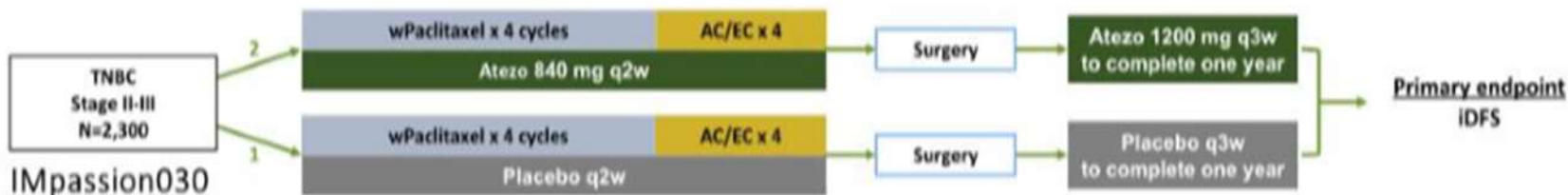
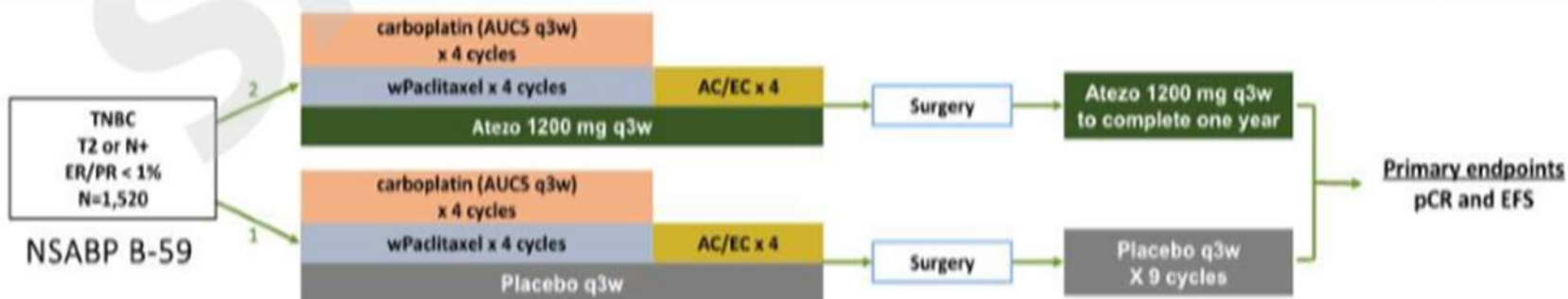
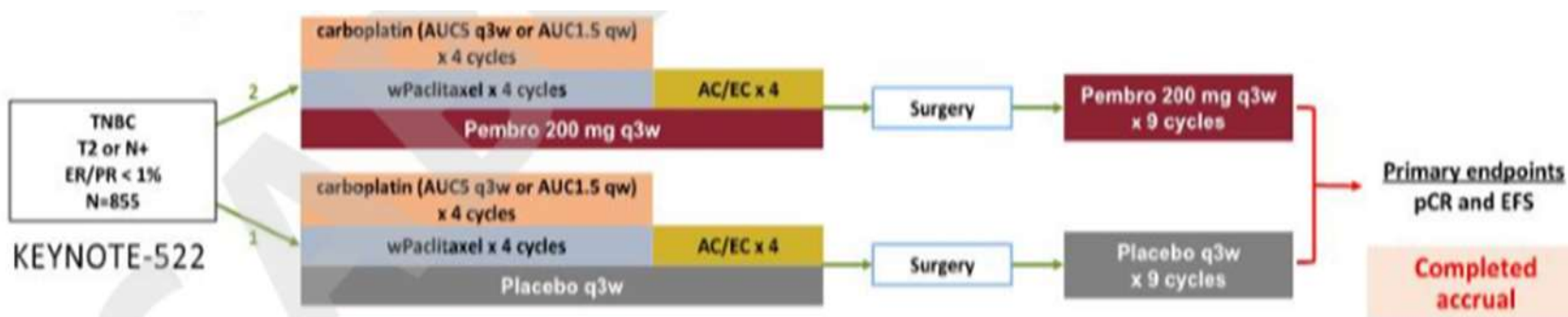
References

- Loibl S et al. Randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab to a taxane-anthracycline containing chemotherapy in triple negative breast cancer (TNBC). ASCO 2019
- Denkert C et al. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. JCO 2015.
- Hagge et al. Interferon Gamma Messenger RNA Signature in Tumor Biopsies Predicts Outcomes in Patients with Non-Small-Cell Lung Carcinoma or Urothelial Cancer Treated with Durvalumab. Clin Cancer Res 2018
- Pagani and Viale. Absolute assignment of breast cancer intrinsic molecular subtype. JNCI 2014

ISPY2 and GeparNUEVO

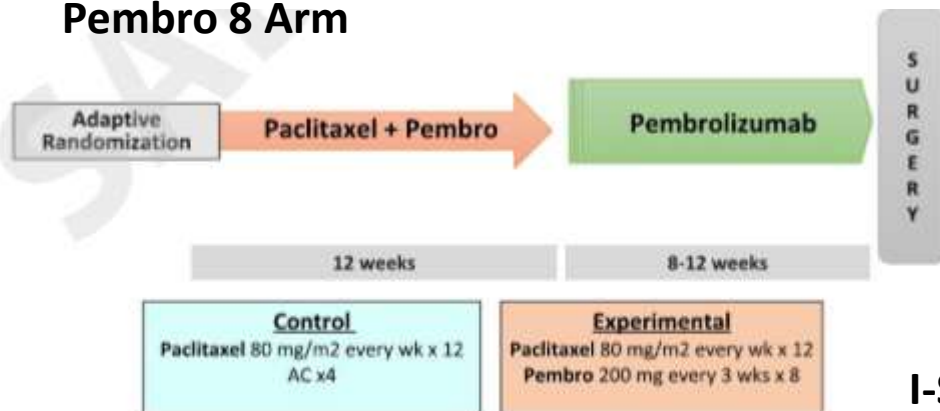
	I-SPY 2	GeparNuevo
Sample size	118	174
Checkpoint inhibitor	Pembrolizumab	Durvalumab
CPI run-in	No	Yes
CPI during anthracycline	No	Yes
pCR rate control	22% (estimated)	44.2%
pCR rate investigational arm	60%	53.4% (61% with window)
EFS HR	--	--

Ongoing neo/adjuvant trials with PD-1/PD-L1 inhibitors



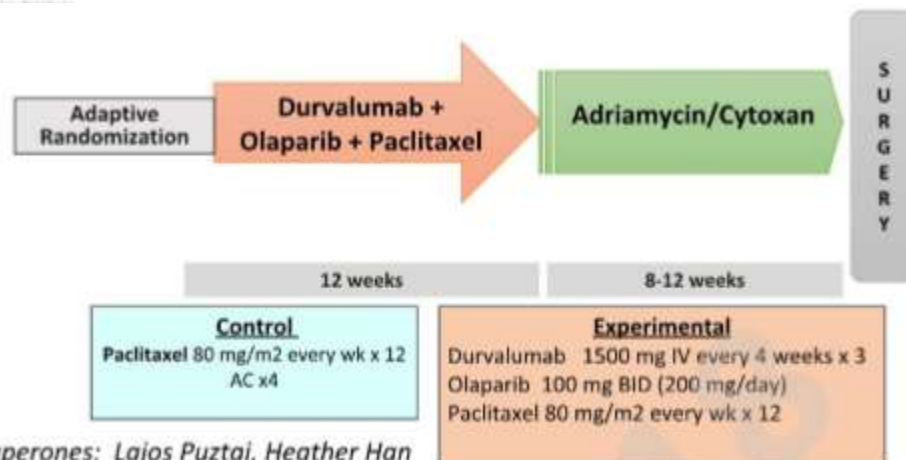
Ongoing neo/adjuvant trials with PD-1/PD-L1 inhibitors

I-SPY2: De-escalating chemotherapy- Pembro 8 Arm



Arm Chaperones: Minetta Liu, Patricia Robinson

I-SPY2: Durva/Olaparib



Arm Chaperones: Lajos Puztai, Heather Han

San Antonio Breast Cancer Symposium, December 4-8, 2018

Pathological complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival, stratified by breast cancer subtypes and adjuvant chemotherapy usage: Individual patient-level meta-analyses of over 27,000 patients.

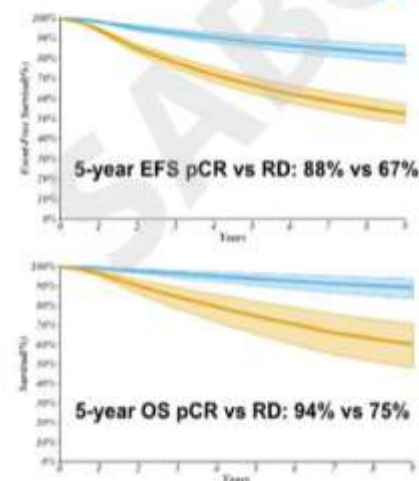
Laura M. Spring MD^{1,3}; Geoffrey Fell MS²; Andrea Arfe MS³; Rachel Greenup MD, MPH⁶; Kerry L. Reynolds MD^{1,3}; Barbara L. Smith MD, PhD^{1,3}; Beverly Moy MD, MPH^{1,3}; Steven J. Isakoff MD, PhD^{1,3}; Lorenzo Trippa PhD^{2,4}; Giovanni Parmigiani PhD^{2,4}; Aditya Bardia MD, MPH^{1,3}

Inclusion criteria were published studies of localized breast cancer with 25 patients or more featuring neoadjuvant chemotherapy that reported pCR (ypT0 ypN0 or ypT0/is ypN0) results as well as recurrence and/or survival based on pathologic outcome.

Total studies included = 52
Number of patients = 27,895

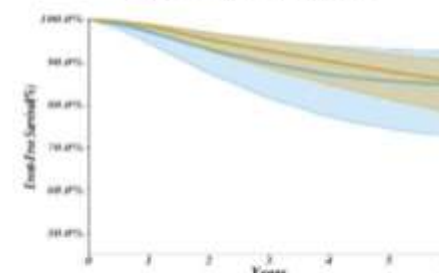
Spring SABC 2018

EFS and OS



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Impact of adjuvant chemotherapy in the setting of pCR



5-year EFS
-pCR followed by adjuvant chemotherapy: 86%
-pCR without additional adjuvant chemotherapy: 88%

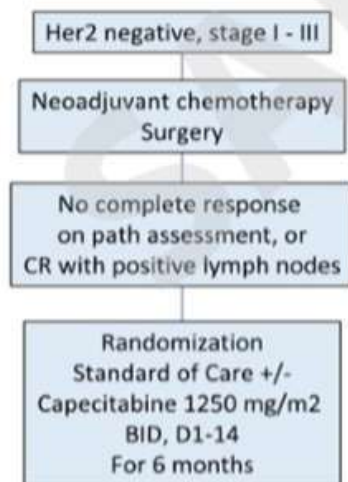
Spring SABC 2018

San Antonio Breast Cancer Symposium, December 4-8, 2018

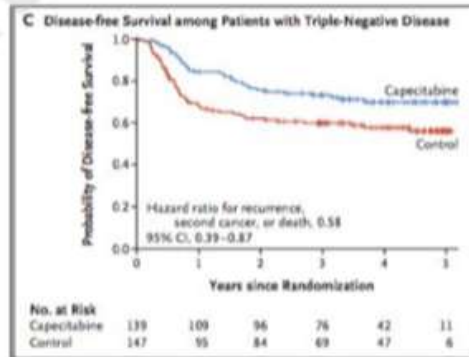
Pathological Response and Survival in Triple-Negative Breast Cancer Following Neoadjuvant Carboplatin plus Docetaxel

Proyecto (Spain), Sara-Laura Torralba¹, José Ángel García-Saenz², Daniel J. Wenz³, María L. Salazar⁴, José María⁵, Francisco Merino⁶, Nicolás José⁷, Giovanni⁸, Agnès Bonaventura⁹, Patricia¹⁰, Pascual¹¹, María del Puerto¹², Ana María¹³, Teresa Pascual¹⁴, María¹⁵, María¹⁶, María¹⁷, María¹⁸, María¹⁹, María²⁰, María²¹, María²², María²³, María²⁴, María²⁵, María²⁶, María²⁷, María²⁸, María²⁹, María³⁰, María³¹, María³², María³³, María³⁴, María³⁵, María³⁶, María³⁷, María³⁸, María³⁹, María⁴⁰, María⁴¹, María⁴², María⁴³, María⁴⁴, María⁴⁵, María⁴⁶, María⁴⁷, María⁴⁸, María⁴⁹, María⁵⁰, María⁵¹, María⁵², María⁵³, María⁵⁴, María⁵⁵, María⁵⁶, María⁵⁷, María⁵⁸, María⁵⁹, María⁶⁰, María⁶¹, María⁶², María⁶³, María⁶⁴, María⁶⁵, María⁶⁶, María⁶⁷, María⁶⁸, María⁶⁹, María⁷⁰, María⁷¹, María⁷², María⁷³, María⁷⁴, María⁷⁵, María⁷⁶, María⁷⁷, María⁷⁸, María⁷⁹, María⁸⁰, María⁸¹, María⁸², María⁸³, María⁸⁴, María⁸⁵, María⁸⁶, María⁸⁷, María⁸⁸, María⁸⁹, María⁹⁰, María⁹¹, María⁹², María⁹³, María⁹⁴, María⁹⁵, María⁹⁶, María⁹⁷, María⁹⁸, María⁹⁹, María¹⁰⁰, María¹⁰¹, María¹⁰², María¹⁰³, María¹⁰⁴, María¹⁰⁵, María¹⁰⁶, 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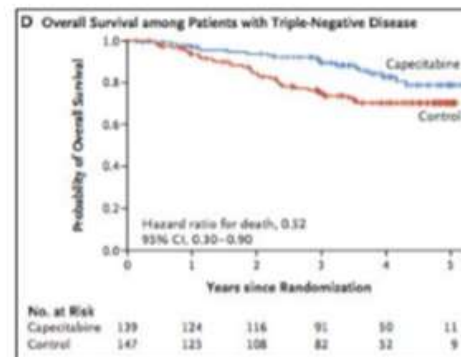
Post-neoadjuvant therapy: Capecitabine in TNBC



CREATE-X Trial (n=910)

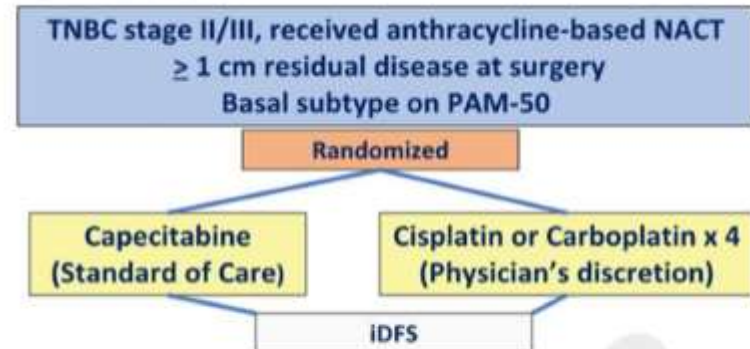


DFS rates at 5 years:
67.6% vs. 73.9%



OS rates at 5 years:
83.6% vs. 89.2%

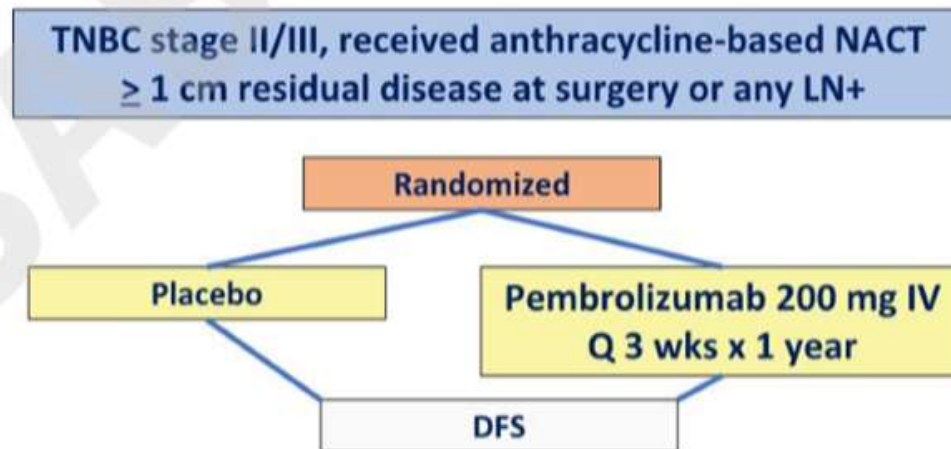
ECOG-ACRIN 1131



Sample size: 562

Post-neoadjuvant therapy: Immunotherapy in TNBC

SWOG 1418



Powered to detect a 33% improvement in DFS (overall and PD-L1+)

Sample size: 1000

NCT02954874 (PI: Puztai)

Minimal Residual Disease: the Next Frontiers

- **Detection**

- Circulating tumor DNA (blood)
- CTCs (blood)
- DTCs (bone marrow)

- **Monitoring**

- Sensitivity/specificity/prognostic significance
- Results disclosure to patients

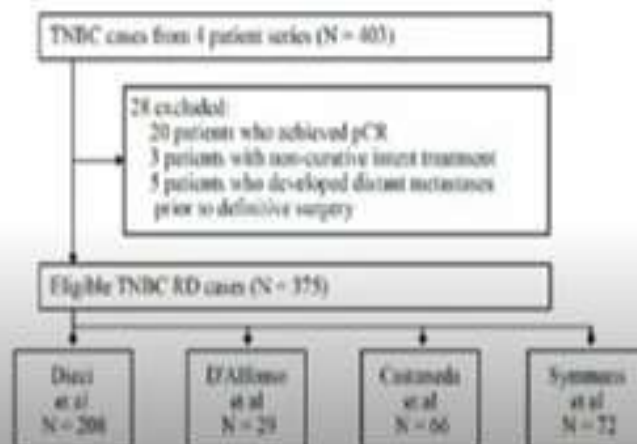
- **Intervention**

- Do TNBC have a dormant phase?
- Best intervention for micrometastatic disease
- Does modulation of surrogate lead to improved survival?

New context in TNBC residual disease setting

Prognostic implications of residual disease tumor-infiltrating lymphocytes and residual cancer burden in triple negative breast cancer patients after neo-adjuvant chemotherapy.

Luen et al, Annals of Oncology, accepted.

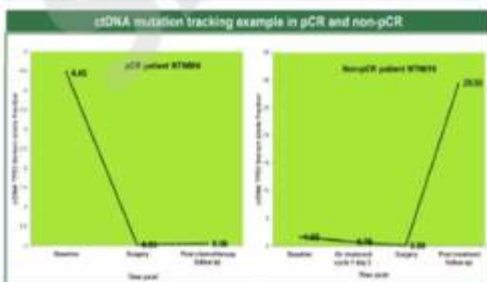


MRD Detection by ctDNA: Pilot Trials

N=6

ctDNA mutations detectable in early stage disease

Concordant with those in primary early stage breast cancers



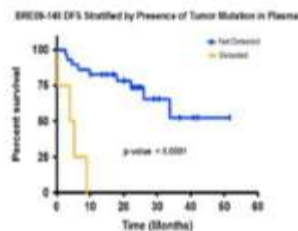
Ademuyiwa, SABCS, 2017

N=38

4 had detectable ctDNA after treatment

Had rapid relapse (< 9 months)

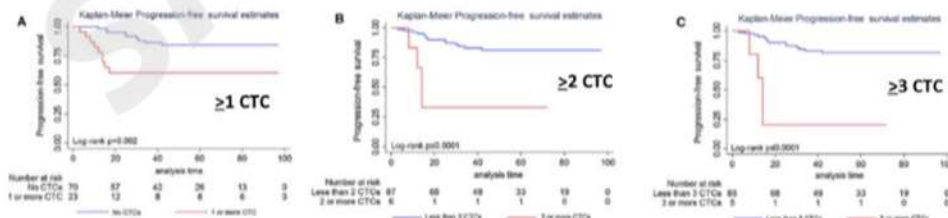
Median DFS: 4.6 mo vs. NR
HR 12.6 (3.06-52.2)



Chen, NPJ Breast, 2017

MRD in TNBC: Detection by CTCs and Outcome

- Evaluated CTCs by CellSearch
- N= 113 patients with stages I-III TNBC at time of definitive surgery.
- Median follow-up: 40 month.
- CTCs were identified in 20 % of patients.



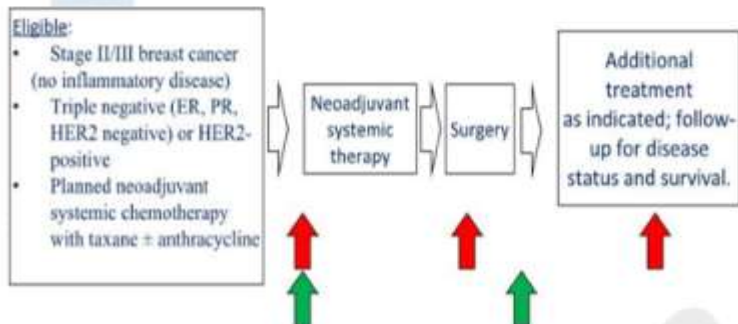
The identification of ≥ 2 CTCs:

Shorter PFS (log rank $P < 0.001$; HR 8.30, 95 % CI 2.61–26.37),
Shorter OS (log rank $P = 0.0004$; HR 7.19, 95 % CI 1.98–26.06)

Karhade, BCRT, 2014

pCR and ptDNA : TBCRC 040 Schema

N=200



- Blood samples:** Baseline/prior to treatment, post-treatment/preoperatively, and postoperatively at 6, 12, 24 and 36 months – then annually thereafter
- Tissue samples:** Tumor tissue from diagnostic biopsy and from the surgical procedure (tumor and/or normal tissue in case of pCR)

NCT02743910
PI: Ben Park

Disseminated tumor cells in the bone marrow

Study	n	Freq	Follow Up (Med)	Hazard Ratio	P-value
Hall, Cancer, 2012	95	26%	24 mos	BCSS: 4.74	0.02
Mathiesen, BCR, 2012	236	26.5%	120 mos	DFS 2.2 BCSS 2.6 OS 2.6	0.005 0.002 0.002

TBCRC 046 "GLACIER Trial"

DTC+ post- NAC

Hydroxychloroquine +/- Gedatolisib

Primary endpoint: Clearance of DTCs

N=80

Launching early 2019

NCT03400254. (PI: DeMichele)

Summary: Challenges in treating early TNBC

- Disease remains high risk, especially if residual disease after NACT
- Optimizing chemotherapy with platinum has some value in some patients – at a price
- Novel therapies improve short-term outcomes, but long-term benefits not yet clear
 - PARP inhibitors
 - Immunotherapy

Summary: Challenges in treating early TNBC

- Post-neoadjuvant trials provide opportunity to escalate therapy in poor responders
 - Smaller trials, faster answers
 - Need biomarkers for treatment selection and time to assess benefits
- Detection and targeting of minimal residual disease is next frontier to improve outcomes for all patients with TNBC

